Important tumor suppressor discovered in immune cells

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With their current study, Prof. Jürgen Ruland (right) and Dr. Tim Wartewig found a new starting point for therapies against lymphoma. Credit: Andreas Heddergott / Technical University of Munich

A team from Technical University of Munich has discovered an "emergency shut-off switch" in immune system T cells. Their results could lead to new therapies against T cell non-Hodgkin's lymphoma triggered by defective immune cells.

In the body, T cells are usually responsible for detecting and killing cancer cells. However, problems can arise when a T cell itself develops a defect in its genome. If the defect affects areas of the genome responsible for cell growth, referred to as oncogenes, the T cell itself can become an uncontrollably dividing tumor cell. In addition, the T cell, an important part of the body's defense against cancer, fails.

This is exactly what occurs in T cell non-Hodgkin's lymphoma. This aggressive form of lymphoma has a very low rate of successful treatment and afflicts approximately one out of every 100,000 persons in Germany. Prof. Jürgen Ruland, Director of the TUM Institute for Clinical Chemistry and Pathobiochemistry is working together with his team to understand the molecular mechanisms of these cancers in order to treat them more effectively.

In their new study, currently published in the journal *Nature*, the scientists were able to show that the defective T cells have an emergency shut-off switch, referred to as a tumor suppressor. They ascertained that the protein PD-1 can turn off defective T cells at an early stage and thus prevent them from becoming tumor cells. The researchers first discovered this function of PD-1 in a mouse model for T cell non-Hodgkin's lymphoma and were also able to explain the mechanism: PD-1 is activated by defects in genes for cell growth, known as oncogenes, and then suppresses the effect of these genes using additional proteins. Thus, it functions as a shut-off switch to prevent the uncontrolled growth of defective T cells.

The scientists also successfully resolved the question of why many T cell

non-Hodgkin's lymphomas are so aggressive, in spite of this protective function. They investigated genetic data sets from 150 patients: "Based on our previous results, we intentionally focused closely on PD-1. In individual groups more than 30 percent of the patients exhibited changes in the regions of the genome that interfered with the production of PD-1. This has disastrous consequences in the tumor—PD-1 no longer functions as an 'emergency shut-off' for them. The diseased T cells can reproduce uncontrollably," says Tim Wartewig, lead author of the study.

"These patients could be helped by medications that reverse the loss of PD-1 signaling and thereby destroy the tumor cells. This type of medication already exists for other forms of cancer. In our opinion, use with T cell non-Hodgkin's lymphoma should also be considered," says Jürgen Ruland. The scientists therefore recommend investigating individual differences in tumors before making decisions about which medication is to be administered.

More information: Tim Wartewig et al, PD-1 is a haploinsufficient suppressor of T cell lymphomagenesis, *Nature* (2017). DOI: 10.1038/nature24649

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